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Attorney Docket No. 6213.200-US
Hoeg-Jensen et al.
Serial No. 09/870,884 Filed May 31, 2001
Via Facsimile No.: 571-273-8300

CLAIM LISTING

1. **(Currently amended)** A crystalline, or soluble aggregate or aggregate-forming insulin derivative, wherein the insulin derivative comprises a lipophilic substituent, and a glucose-sensing group, wherein the glucose-sensing group is an aryl boronate group, **wherein the glucose-sensing group is built into a substituent capable of effecting the formation of high molecular aggregates, and wherein the substituent causing aggregation is a lipophilic group**.

2. (Original) The insulin derivative of claim 1, wherein the insulin derivative is a natural insulin or an insulin analogue.

3. (Original) The insulin derivative of claim 1, having a glucose affinity in the range of 0.01 μM to 10 mM.

4. (Cancelled)

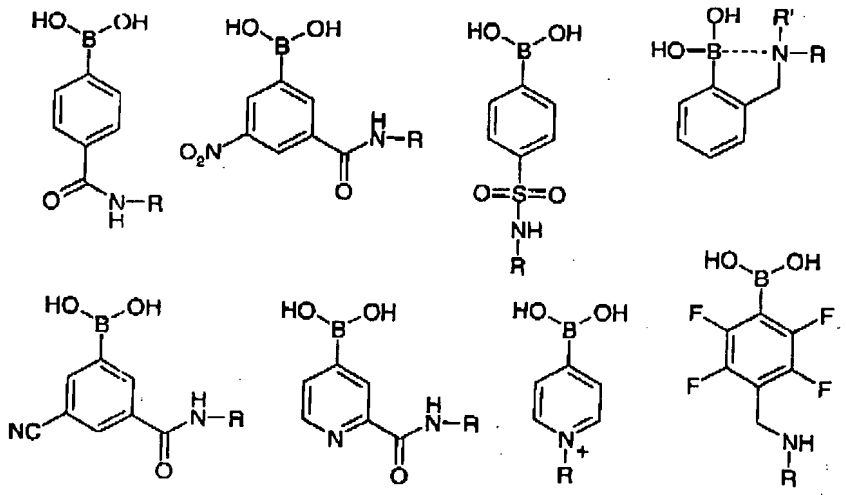
5. (Previously presented) The insulin derivative of claim 1, wherein the aryl boronate group comprises an electron-withdrawing substituent.

6. (Previously presented) The insulin derivative of claim 5, wherein the electron-withdrawing substituent is selected from the group consisting of sulfo, carboxy, nitro, cyano and fluoro.

7. (Original) The insulin derivative of claim 5, which has an amino group in proximity to the boronate moiety in the form of a 2-aminomethylarylboronate.

8. (Original) The insulin derivative of claim 7, which has an amino group within 2.0 Ångstrom from the boron atom.

9. (Previously presented) The insulin derivative of claim 1, wherein the aryl boronate group is selected among the following groups, wherein R designates the insulin moiety, lipophilic substituent and an optional linker, and R' designates hydrogen, methyl, ethyl, propyl, isopropyl or benzyl:



10. (Previously presented) The insulin derivative of claim 1, wherein the arylboronate group is attached to the insulin moiety via the α-amino group of GlyA1 or PheB1, or via the ε-amino group of a Lys residue at position B3, B28, B29 or B30 or an Orn residue, a Dap residue, a Dab residue, an Asp residue or a Glu residue at position B30.

11. (Previously presented) The insulin derivative of claim 1, wherein the arylboronate group is attached to the insulin moiety via a linker.

12. (Original) The insulin derivative of claim 11, wherein the linker is selected from the group consisting of γ-glutamyl, α-glutamyl, β-aspartyl, α-aspartyl, β-alanine, piperazine and aniline.

13. (Previously presented) The insulin derivative of claim 1, wherein the glucose sensing aryl boronate is a part of the amino acid residue in position B26 of the insulin moiety.

14. (Previously presented) An insulin derivative comprising a glucose-sensing group, wherein the glucose sensing group is a peptide or pseudopeptide, optionally comprising Asn, Trp, His, Asp, Arg or a boronate containing amino acid.

15. (Original) The insulin derivative of claim 14, wherein the glucose sensing peptide is comprised within the residues 26-30 of the B-chain, optionally extended beyond the C-terminal residue 30 of the B-chain.

16. **(Cancelled)**

17. **(Cancelled)**

18. **(Currently amended)** The insulin derivative of claim **1** **[[17]]**, wherein the lipophilic group is a derivative of a bile acid selected from the group comprising lithocholic acid, hyocholic acid, hyodeoxycholic acid and chenodeoxycholic acid.

19. (Original) The insulin derivative of claim 18, wherein the lipophilic group is attached to the insulin moiety via a γ-glutamyl, α-glutamyl, β-aspartyl, α-aspartyl or β-alanine spacer.

20. **(Currently amended)** The insulin derivative of claim 1 [[17]], wherein the lipophilic group is a derivative of an α,ω-dicarboxylic acid having from 10 to 30 carbon atoms.

21. (Previously presented) An insulin derivative according to claim 1 comprising a monosaccharide, disaccharide, or trisaccharide group, capable of binding to an insulin derivative having a glucose-sensing group.

22. (Previously presented) The insulin derivative of claim 1, further comprising a monosaccharide, disaccharide, or trisaccharide substitution.

23. (Original) The insulin derivative of claim 1, capable of forming water soluble, high molecular aggregates having a molecular weight > 150 kDa.

24. (Original) A water soluble, protracted, glucose dependent pharmaceutical composition comprising one or more of the insulin derivatives of claim 1.

25. (Original) A soluble, biphasic-acting insulin preparation comprising one or more of the insulin derivatives of claim 1, mixed with human insulin or an insulin with rapid onset of action, such as human insulin or des(B30) human insulin or Asp^{B28} human insulin or $Lys^{B28}Pro^{B29}$ human insulin or $Gly^{A21},Lys^{B3},Ile^{B28}$ human insulin, or $Asp^{A21},Lys^{B3},Ile^{B28}$ human insulin in ratios from 10:1 to 1:10.

26. (Previously presented) A soluble insulin preparation comprising an insulin derivative according to claim 1, characterized by having a rate of absorption from an injected depot,

which rate of absorption increases as the glucose concentration in the tissue increases, and decreases as the glucose concentration decreases.

27. (Original) Crystalline preparations of one or more of the insulin derivatives of claim 1.

28. (Original) A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of the insulin derivative of claim 1.

29. (Previously presented) A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of the insulin derivative of claim 14.

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RESPONSE

The examiner states in the Office Action Summary that claims numbered 1-3 and 5-29 are pending in the application; claims numbered 1-3, 5-16, 21-26, 28 and 29 are rejected; claims numbered 17-20 and 27 are objected to.

Applicant thanks Examiner Russel for the helpful discussion held with the undersigned on July 26, 2007. Applicant has amended claims numbered 1, 18 and 20, and has cancelled claims numbered 16 and 17, which incorporates Examiner Russel's suggestions and is anticipated to place the presently pending claims in condition for allowance.

(1) The examiner states claims numbered 1-3, 5-16, 21-26, 28 and 29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-11, 14-28 abd 31-35 of copending Application Serial No.: 10/307,678 (the "'678" application, Attorney Docket No. 6440.200-US). The conflicting claims are not identical, however they are patentably indistinct from each other because the claims of the '678 application anticipate the present claims.

Applicant believes the present amendment will moot the provisional rejection on the ground of nonstatutory obviousness-type double patenting. However, if necessary, Applicant will timely file a Terminal Disclaimer upon identification of allowable claims.

(2) The examiner states claims numbered 1-3, 5, 6, 11, 16, 21-24, 26 and 28 are rejected under 35 U.S.C. §102(b) as being anticipated by Miyazaki et al. (U.S.Patent No. 5,478,575). Miyazaki et al. teach sugar-responsive polymer complexes which are used to treat diabetes.

Applicant has amended claim number 1 to incorporate the limitations of claims numbered 16 and 17.

Applicant respectfully requests reconsideration and withdrawal of the rejection of claims numbered 1-3, 5, 6, 11, 16, 21-24, 26 and 28 under 35 U.S.C. §102(b).

(3) The examiner states claim number 10 is rejected under 35 U.S.C. §102(b) as being anticipated by Miyazaki et al. (U.S.Patent No. 5,478,575) as applied against claims numbered

1-3, 5, 6, 11, 16, 21-24, 26 and 28, and further in view of PCT Application Publication Number 84/01896.

Applicant has amended claim number 1 to incorporate the limitations of claims numbered 16 and 17.

Applicant respectfully requests reconsideration and withdrawal of the rejection of claim number 10 under 35 U.S.C. §102(b).

(4) The examiner states claim number 25 is rejected under 35 U.S.C. §103(a) as being obvious over Miyazaki et al. (U.S.Patent No. 5,478,575) as applied against claims numbered 1-3, 5, 6, 11, 16, 21-24, 26 and 28, and further in view of PCT Patent application Publication Number 99/21888.

Applicant has amended claim number 1 to incorporate the limitations of claims numbered 16 and 17.

Applicant respectfully requests reconsideration and withdrawal of the rejection of claim number 25 under 35 U.S.C. §103(a).

(5) The examiner states claims numbered 17-20 and 27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant has amended claim number 1 to incorporate the limitations of claims numbered 16 and 17, and cancelled claims numbered 16 and 17. Applicant has amended claims numbered 18 and 20 to correct the dependency of the claims.

Applicant respectfully requests reconsideration and withdrawal of the objection to claims numbered 17-20 and 27.

The examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

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Respectfully submitted,

Date: July 26, 2007

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